

**Integrated management of childhood illness indicators of childhood tuberculous meningitis at a tertiary hospital in the Western Cape Province of South Africa**

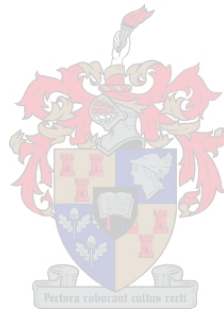
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## **Declaration**

I hereby declare that this research study was undertaken to fulfil my requirements for a MMed degree at Stellenbosch University and is my own original work. I also declare that I have not previously submitted this task to any other university.

All sources used in this study have been acknowledged and cited with complete references.

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**Dr M Grantham**

**February 2015**

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**Abstract**

**BACKGROUND:** Tuberculous meningitis (TBM) is the most common type of bacterial meningitis in the Western Cape of South Africa. Early clinical diagnosis is notoriously difficult and often delayed, with disastrous consequences for patients. The Integrated Management of Childhood Illness (IMCI) strategy is the primary child-care approach of choice for South Africa which ensures accurate assessment of sick children using simple yet reliable clinical signs at the first contact level.

**METHODS:** A retrospective observational study of 30 consecutively diagnosed TBM children at Tygerberg Children's Hospital with the aim of identifying IMCI clinical indicators which would warrant urgent referral and earlier treatment

**RESULTS:** Of the 30 TBM children, 17 male, median age 35 months, 6 (20%) presented with stage I TBM, 6 (20%) with stage II TBM and 18 (60%) with stage III TBM. The median number of healthcare visits prior to hospital admission was 4.0 (range 1-6). At the 1<sup>st</sup> healthcare visit, 10 (33%) of TBM children had at least one IMCI general danger sign, 22 (73%) had TB-specific signs/symptoms and 18 (60%) "TBM-specific signs/symptoms".

**CONCLUSION:** If correctly applied, IMCI clinical indicators would ensure earlier diagnosis of TBM.

## Introduction

Tuberculosis (TB) remains a deadly global burden with an estimated 9.0 million new cases and 1.5 million deaths in 2013.<sup>1</sup> As TB is preventable the high mortality is concerning. Of the new cases, 3.5% have multi-drug resistant (MDR) TB and 13 % have HIV co-infection.<sup>1</sup> South Africa has one of the highest tuberculosis (TB) burdens in the world and was one of the top 6 countries with the largest number of incidence cases in 2013, no doubt contributed to by high burdens of MDR-TB and HIV co-infection.<sup>1</sup> Recently the reported incidence in SA was 860/100 000 (up to 993/100 000 in certain areas), compared to a global incidence of 126/100 000.<sup>1,2</sup>

Tuberculous meningitis (TBM) represents the most severe extrapulmonary manifestation of TB. It is the most common cause of pediatric bacterial meningitis in the Western Cape Province of South Africa.<sup>3</sup> Outcome in childhood TBM is determined by severity of disease at onset (stage of disease). Early TBM (stage I) is almost always associated with a favourable outcome whilst advanced TBM (stage III) has a morbidity of 80% and a mortality as high as 60%.<sup>4</sup> In contrast to other forms of bacterial meningitis, TBM has a chronic course and opportunities for earlier diagnosis and intervention are often missed, with dire consequences. The onset of TBM is mostly insidious (days to weeks), and the early symptoms are non-specific, such as cough, low grade fever, vomiting, irritability and general listlessness.

Integrated Management of Childhood Illness (IMCI) was a strategy developed by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) in the 1990's in response to persistently high children under-five mortality rates.<sup>5,6</sup> It involves implementation of a strategy aimed at identifying common childhood illnesses in resource-poor countries. Early detection of serious illnesses in resource limited settings allows for

early referral and thus reduction in morbidity and mortality. It is mainly aimed at prevention and management of the leading causes of serious illnesses.<sup>5,6</sup>

IMCI has been implemented globally in third world countries and adapted to different areas to cover the most serious location-specific illnesses. Currently more than 100 countries, including 44 sub-Saharan African countries, have implemented IMCI screening strategies.<sup>2</sup> Adaptations of the generic IMCI were made to suite the South Africa epidemiological profile by the removal of malaria and the addition of HIV/AIDS and asthma guidelines.

The focus is on the first point of contact with the patient; usually a primary-level care setting. Algorithms were devised for detection of key symptoms and signs, allowing triage and appropriate management of children under 5 and if indicated, referral to secondary and tertiary facilities.<sup>1,5,7</sup> Case management is guided by algorithms checking for danger signs, asking questions about common conditions, assessing nutrition and immunization status. This is followed by classification and specific treatment. The IMCI case management process is presented in a series of chart booklets with easy to follow algorithms and health care workers are trained to follow the algorithms.<sup>1,7</sup>

IMCI screening for TB is allowed for in locations with high TB burden. Where there is an adult household contact that has been diagnosed with, or treated for, pulmonary TB in the previous 12 months in addition to at least 1 of: 1) persistent, non-remitting cough or wheeze >14 days 2) documented weight loss or poor weight gain during the previous 3 months 3) fatigue or reduced playfulness 4) daily fever >14 days, the child is notified and treatment instituted for TB.

The IMCI criteria for diagnosing meningitis include abnormal level of consciousness, convulsions, high fever without a clear cause, vomiting or irritability. Additional criteria in infants are poor feeding, lethargy and apnoea. Additional criteria in older children are photophobia, headache and neck stiffness.<sup>8,9</sup> These criteria are not specific for TBM, and are covered by general IMCI guidelines previously listed. The 2013 WHO guidelines for the management of common childhood illnesses, which is consistent with the IMCI guidelines for outpatient management of sick children, has TBM-specific criteria.<sup>10</sup> TBM should be considered if any one of the following is present: 1) fever persisting for >14 days 2) fever persisting >7 days and an adult household TB contact 3) known HIV infection or exposure 4) depressed level of consciousness despite treatment for bacterial meningitis 5) a chest radiograph suggestive of pulmonary TB 6) CSF with an elevated white cell count, lymphocyte predominance, increased protein and decreased glucose. As the IMCI criteria are intended for use in primary-level healthcare facilities, only criteria 1 to 4 are applicable.

## **Hypothesis**

The IMCI referral criteria are useful for the early identification of children with suspected TBM.

## **Objectives**

- 1.1. To determine the number of healthcare visits prior to diagnosis of TBM, where IMCI referral criteria could potentially be applied
- 1.2. To identify clinical indicators of TBM by examining components of the IMCI referral criteria for meningitis in a group of hospitalized children with TBM.
- 1.3. To determine whether 'TB-specific' IMCI criteria can identify childhood TBM suspects.

1.4. To determine whether ‘TBM-specific’ IMCI-aligned criteria can identify childhood TBM suspects.

1.5. To determine whether IMCI ‘general danger signs’ can identify childhood TBM suspects.

## **Methodology**

This retrospective observational pilot study was conducted at Tygerberg Children’s Hospital, a tertiary referral centre in Cape Town, South Africa. Thirty children diagnosed with TBM aged 3 months to 5 years were enrolled between September 2012 and June 2013. After interviewing the primary caregiver, all children were assessed and classified according to the IMCI algorithm.

### ***TBM case definition***

TBM was clinically diagnosed when CSF changes were suggestive of TBM (clear appearance and pleocytosis 10-500/ $\mu$ l and/or increased protein >1g/dl, and/or decreased glucose defined as <2.2mmol/l or CSF to serum ratio of <50%) and at least two of the following criteria were met: 1) recent contact with an infectious TB source case or a positive tuberculin skin test (TST), 2) a chest x-ray suggestive of TB, 3) computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating features of TBM (hydrocephalus, meningovascular enhancement, infarction, and/or granuloma/s).<sup>11</sup>

TBM was staged according to revised British MRC criteria as: Stage I) Glasgow Coma Scale (GCS) of 15 and no focal neurology, Stage II) GCS of 15 plus focal neurology or GCS of 11-14 with/ or without focal neurology and Stage III) GCS <11.<sup>4,12</sup>

***Other definitions******General IMCI guidelines (addendum 1):<sup>8</sup>***

- 1) *General danger signs/ critically ill child algorithm.* This enquires about poor feeding, vomiting, convulsions, lethargy, and reduced level of consciousness.
- 2) *Does the child have fever?algorithm.* Enquires about duration of fever, and includes checking for neck stiffness and a bulging fontanelle.
- 3) *Malnutrition/anaemia algorithm.* Detects growth faltering which may lead to TB screening. Weight loss has been considered an early warning sign to suspect TB , however the algorithm does not prompt IMCI-trained healthcare workers to exclude this diagnosis.
- 4) *HIV infection algorithm.* May lead on to screening for TB.
- 5) *Screening for TB algorithm.* TB is notified and treatment initiated when an adult household TB contact within the last 12 months is present with 2 or more of: i) persistent cough longer than 2 weeks ii) documented weight loss or poor weight gain for 3 months iii) reduced playfulness iv) fever longer than 2 weeks.

***IMCI-aligned TBM-specific guidelines for management of common childhood illnesses (addendum 2):<sup>10</sup>***

- 1) Fever >7 days with a known adult household TB contact within the last 12 months
- 2) Fever >14 days without a known TB contact
- 3) Known HIV infection or exposure
- 4) Depressed level of consciousness

**Statistical analysis**

Statistical analysis was carried out using SPSS version 21 (SPSS Inc, Chicago, IL, USA). For descriptive purposes, frequencies were determined for categorical variables, with median and



interquartile range reflected for continuous variables. Sensitivity of the individual general IMCI guidelines and IMCI TBM-specific criteria was determined. The percentage of cases that were identified at first assessment was determined.

The study was approved by the Human Research Ethics Committee of Stellenbosch University, South Africa (study nr. S13/08/129).

## **Results**

Thirty children, 17 males, 1 HIV infected, mean age 3.47 (range 5-60 months) were included in the study. The mean number of health care visits prior to admission to hospital was 3.47 (range 1-6) Twenty- four (80%) of patients had stage 2 or 3 TBM (table 1).

The majority of patients (29/30) included in this study had at least one “sign of TB” at first visit when retrospectively applying the IMCI criteria (table 3). These included 20 (67%) with cough persisting longer than 14 days, 7(23%) with fever persisting longer than 14 days, 20 (67%) with persistent cough longer than 2 weeks, 21(70%) with an adult household TB contact within the previous 12 months and 24 (80%) with poor weight gain or loss of weight in the previous 3 months. Twenty-two patients (73%) had an adult household TB contact and >2 ‘TB-specific’ signs, enabling them to be notified and treated for TB. However only 1 patient was correctly classified and identified. Unfortunately this child was lost to follow up and presented later with TBM. Eighteen patients (60%) had at least one “TBM-specific” feature (table 3). These included 18 (60%) with fever persisting >7 days and an adult household TB contact within the previous 12 months, 7 (23%) with fever persisting longer >14 days, 1 (3%) with known HIV infection or exposure and 1 (3%) with depressed level of consciousness.

Out of 10 patients presenting with general danger signs at first visit (when retrospectively applied), only 1 presenting with seizures at the first visit was referred immediately as per IMCI guidelines. Figure 1 illustrates the timing of referral for danger signs in those unreferred at the first visit to a healthcare facility. Figure 2 illustrates those identified with general danger signs per healthcare visit (1 through 6). In the 10 patients with general danger signs at 1<sup>st</sup> healthcare visit, 2 were eventually diagnosed with stage 2 TBM and 8 patients with stage 3 TBM. Eight of the ten patients would have been classified as stage 1 TBM according to the initial presenting symptoms at first visit to a healthcare facility. The presence of general danger signs were significantly associated with stage 2 and 3 TBM ( $p=0.05$ ).

The IMCI TB-specific guidelines were 73% sensitive in identifying children for TB notification and treatment. All children with general danger signs at 1<sup>st</sup> visit also fulfilled the TB-specific criteria for TB notification and treatment. The IMCI-aligned TBM-specific criteria were 60% sensitive in identifying children with TBM.

## **Discussion**

An important factor that differentiates the symptoms of TBM from common illnesses such as influenza is their persistence, although this feature is often missed if a patient does not see the same health professional consistently. The presence of vomiting, without diarrhoea, indicative of raised intracranial pressure is sometimes mistakenly attributed to gastroenteritis whilst the presence of a household TB contact or crossing of weight percentiles in the Road-To-Health-Booklet is often overlooked.

Despite efforts by the WHO and UNICEF to improve health in resource-constrained countries, morbidity and mortality of preventable diseases remain a burdensome problem, with lack of resources being the main obstacle.<sup>5,6</sup> IMCI is a valuable tool in detecting more serious underlying medical conditions and if management, follow up and referral criteria are implemented correctly, it could potentially have a major impact on the improvement of health and well-being.

Patients diagnosed with TBM at a tertiary level facility in the Western Cape had multiple missed opportunities before an eventual diagnosis was made, with up to 6 visits to health care facilities before a diagnosis of TBM was made. The prognosis of TBM closely correlates to the stage of illness at presentation and length of time to initiation of treatment.<sup>13</sup> It is obvious that early detection of TBM (stage 1) would lead to reduced morbidity and mortality.

A large retrospective cohort study done performed at Tygerberg Children's Hospital concluded that TBM mainly affects young children <5 years of age, that young age and non-specific signs may contribute to delayed diagnosis and that poor follow up of children <5 years of age with of proven adult TB household contacts may lead to missed prophylaxis.<sup>11</sup> The study further advised that weight loss, fever, vomiting and a household TB contact warranted further investigation to exclude early TBM, and thereby prevent advanced TBM stage of disease.<sup>11</sup>

Our study reiterates these findings, as 73% of our patients had "signs of TB" as defined by the IMCI criteria. This emphasizes that IMCI is a valuable tool in detecting early TB, as well as children without disease but exposed to positive adult household contacts. However, poor application of the IMCI algorithms lead to missed opportunities for early diagnosis and treatment. When applying the IMCI-aligned TBM specific signs, 60% of patients fulfilled

criteria at first presentation. However, these guidelines were intended for hospital use and chest radiograph and CSF findings were excluded in our primary level healthcare cohort. However, the level of detection is less than the higher sensitivities of the uniform research case definition for TBM in children.<sup>14</sup>

General danger signs, as described in the IMCI criteria, together with signs of TB, has potential use in identifying advanced stage TBM as vomiting (especially without diarrhoea), poor feeding, convulsions, lethargy or decreased level of consciousness are sensitive indicators of intracranial pathology. Suspicion, early referral and management of TBM at this stage could lead to morbidity and mortality reduction.<sup>3,4,11</sup>

Children under the age of 5 are most at risk of contracting TB from an adult household TB contact and screening is vital to detecting and treating early disease or implementing prophylaxis.<sup>15</sup> Contact investigation is a strategy recommended globally in an attempt for early detection and prevention by means of prophylaxis or early treatment.<sup>16</sup> The success of screening programmes is directly linked to ensuring sufficient resources and staffing in busy primary-level care facilities.

As shown in the study, TB-specific IMCI criteria are sensitive in detecting early TBM. Using the TB-specific criteria in addition to a general danger sign at 1<sup>st</sup> healthcare visit, and thereby implying possible central nervous system involvement (TBM) identified far less children than the IMCI-aligned TBM-specific criteria. Inclusion of the IMCI-aligned TBM-specific criteria (fever persisting for >14 days, fever persisting >7 days with an adult household TB contact, known HIV infection or exposure and depressed level of consciousness) in the South African

IMCI guidelines is warranted to avoid missing early cases of TBM, especially in the local setting, where TBM is the most common form of bacterial meningitis.<sup>3,17</sup>

Regular IMCI training sessions in the primary-care setting is a cheap and effective tool to detect and manage TBM early in the stage of disease, with the knock-on effects of reduced morbidity, mortality and health-care costs. Studies on evaluation of IMCI noted that training and understanding of IMCI was generally good, however implementation wanes with time with lack of IMCI-specific supervision at busy primary-care facilities.<sup>18</sup>

Effectively, the early warning signs for stage 1 TBM may be detected with criteria scattered throughout the various current IMCI algorithms but would call for a sense of vigilance on the part of IMCI practitioners. IMCI trained health care practitioners working in busy primary level care facilities and have been trained to follow specific algorithms which have been found to be useful if implemented correctly.

A limitation of our study is the potential of recall bias when questioning the caregivers. Further limitations are the small number of patients assessed, however this was a pilot study, as well as the lack of non-TBM (other form of meningitis) and non-meningitis with pulmonary TB control groups as this would have allowed diagnostic accuracy to be determined. Our study only had 1 patient (3%) with HIV co-infection. Karande et al. also found low numbers (6.5% of 123 children) of clinically diagnosed TBM had HIV co-infection (6.5% of 123 children).<sup>19</sup>

If using stage of TBM as a proxy outcome measure, the delayed diagnosis resulted in worse outcome for the majority of patients in this study, as 60% of patients were diagnosed as stage

III TBM (including 20% with infarction). Our study focused on symptomatology at presentation and is limited by the absence of data on longterm sequelae. A follow-up study including motor, seizure, cognitive and behavioural outcome will strengthen the findings of the current study.

In conclusion, a high index of suspicion and low threshold for early screening of TBM is required in high-burden settings, such as South Africa. IMCI criteria are sensitive in detecting TB and TBM and may be a valuable, cost-effective tool in reducing the burden of TB and TBM if implemented correctly. Our study recommends that the IMCI-aligned TBM-specific criteria be added to the TB guidelines in the local IMCI booklet. Supervision and reinforcement of IMCI implementation at primary health care facilities is warranted.

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**Table 1. Patient demographics, healthcare visits and TBM stage.**

Total no. of patients	30
Male gender, n(%)	17 (57)
Mean age (range) in months	32.1
Median age (range) in months	35.0 (5.0-60.0)
Mean no. of healthcare visits prior to admission	3.47
Median no. of healthcare visits prior to admission	4.0
<b>TBM stage at admission, n (%)</b>	
Stage 1	6 (20)
Stage 2	6 (20)
Stage 3	18 (60)

TBM= tuberculous meningitis, n= number

**Table 2. General IMCI symptoms and signs at first healthcare visit**

<b>Symptoms and signs</b>	<b>n (%)</b>
Fever	27 (90)
Vomiting	7 (23)
Diarrhoea	2 (7)
Cough	21 (70)
Upper respiratory tract infection	1 (3)
Loss of appetite	1 (3)
Weight loss	23 (77)
Lethargy	3 (10)
Convulsions	2 (7)
Cervical lymph nodes	1 (3)
Depressed level of consciousness	1 (3)
Focal neurological deficit	1 (3)
Only 1 symptom/sign	30 (100)
2 symptoms/signs	28 (93)
≥ 3 symptoms/signs	24 (80)

IMCI= integrated management of childhood illness, n= number

**Table 3. IMCI ‘TB-specific’<sup>8</sup> and IMCI-aligned ‘TBM-specific’<sup>10</sup> clinical features at 1<sup>st</sup> healthcare visit.**

<b>Presenting symptoms/signs</b>	<b>n (%)</b>
<b><u>‘TB-specific’</u></b>	
Adult household TB contact	21 (70)
1. Cough >14 days	20 (67)
2. Fever >14 days	7 (23)
3. Loss of weight/ poor weight gain >3 months	24 (80)
4. Reduced playfulness	3 (10)
Number of patients with at least 1 ‘TB-specific’ feature	29 (97)
Number of patients with $\geq 2$ ‘TB-specific’ features (prompting notification and treatment)	22 (73)
<b><u>‘TBM-specific’<sup>10</sup></u></b>	
Fever >7 days and adult household TB contact	18 (60)
Fever >14 days	7 (23)
Known HIV infection or exposure	1 (3)
Depressed level of consciousness	1 (3)
Number of patients with at least 1 ‘TBM-specific’ feature	18 (60)
Number of patients with at least >1 ‘TBM-specific’ feature	12 (40)

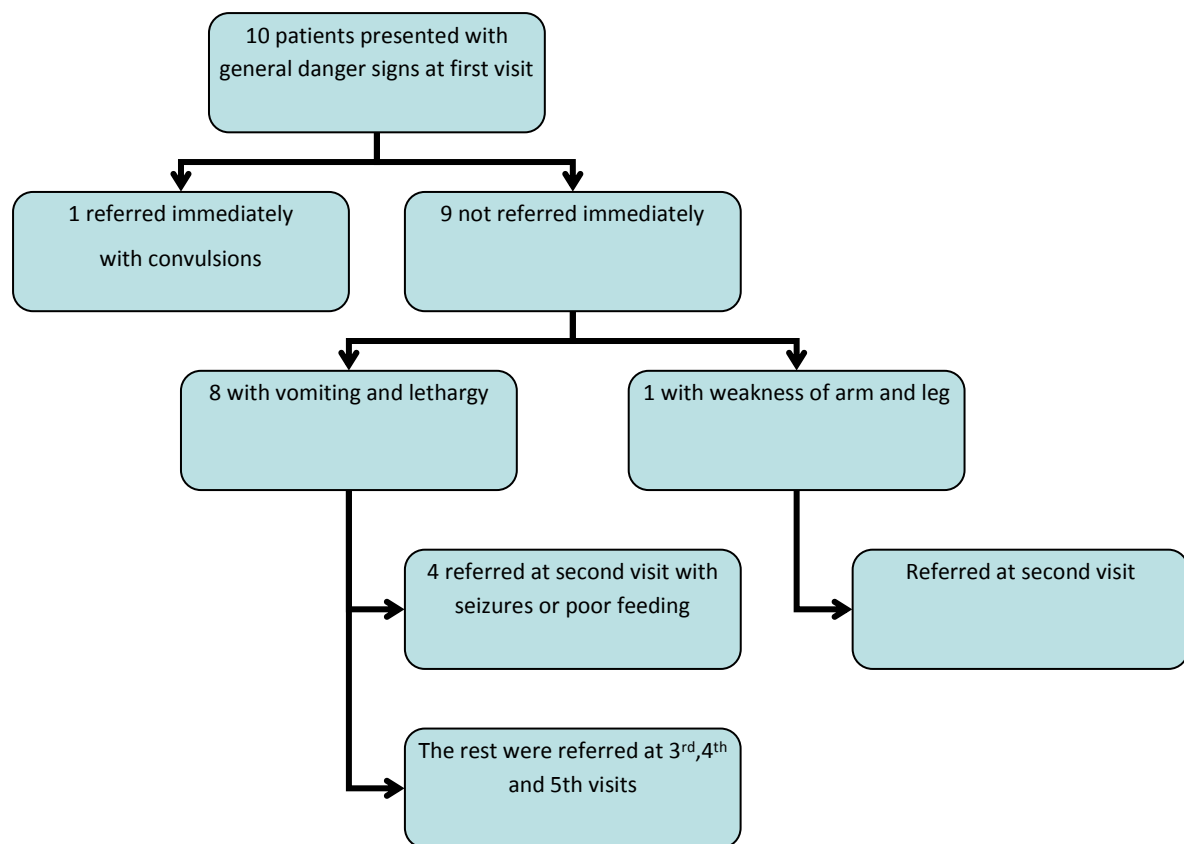
IMCI= integrated management of childhood illness, TB= tuberculosis, TBM= tuberculous meningitis, n= number, HIV= human immunodeficiency virus

**Table 4. IMCI general danger signs and treatment instituted at 1<sup>st</sup> and 2<sup>nd</sup> healthcare visit**

Symptoms/signs	n/N (%)	
	1 <sup>st</sup> visit	2 <sup>nd</sup> visit
Poor feeding	1/30 (3)	0
Vomiting	7/30 (23)	2/29 (7)
<i>Vomiting without diarrhoea</i>	5/30 (17)	
Convulsions	2/30 (7)	1/29 (3)
Lethargy or depressed level of consciousness	3/30 (10)	4/29 (14)
No. of patients with at least 1 general danger sign at healthcare visit	10/30 (33)	6/29 (21)
Treatment instituted according to the presence of general danger signs	1/10 (10)	5/6 (83)

IMCI= integrated management of childhood illness

**Figure 1. Management flow diagram of children presenting with general danger signs at 1<sup>st</sup> presentation**



**Figure 2. Flow diagram of children presenting with general danger signs per healthcare visit**

